

# **Improving the results of colorectal surgery**

**Doctoral thesis (PhD)**

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## **I. Introduction**

The objective of my research is to enhance the efficacy of colorectal surgery and to minimise complications. This topic is of paradigm-shifting importance, as the successful completion of a surgery is not merely a transient success; it also serves to ensure long-term cancer-free survival of the patient and the quality of life they can expect. As in many areas of healthcare, the surgical professions have been affected by significant changes, particularly technological changes, in recent decades and will continue to be affected in the future.

It is imperative that surgeons remain informed of developments in order to provide patients with the most effective and optimal care available. My motivation as a researcher, in light of the above, was to learn new techniques and to study their effectiveness. I also took a scientific approach to the study of readily available factors that are or are perceived to be important for patient recovery. These results naturally raise new questions, which will stimulate further work to analyse and research, and to better understand the background to these results in the future.

## **II. Theoretical background**

### **II.1. Number of colorectal surgeries**

It is estimated that nearly 450,000 cases of colorectal cancer are diagnosed in Europe each year. Hungary is ranked third in the EU for this type of cancer in both sexes. According to the National Cancer Registry, 9,000 to 10,000 cases of colorectal cancer are diagnosed annually, with a slight upward trend. It is important to note that colorectal surgery can be performed for a number of indications other than malignant processes.

According to the available data, approximately 7,000 colorectal surgeries are performed in Hungary every year.

## II.2. Minimally invasive surgical techniques and optimisation of perioperative management

The short-term outcomes of the minimally invasive technique, including a lower surgical site infection rate, lower pain, faster recovery, and less need for transfusion, were confirmed. However, comparison of oncological outcomes required a longer time, but the equivalence of MIS was demonstrated. The risk of SSI with the open surgical technique is higher than with laparoscopy. Consequently, it is of paramount importance to conduct a thorough examination and visualization of the surgical site in open surgery. Nevertheless, it is possible for wound infections to occur despite the most meticulous care. The elements of this care are summarized in a package of treatment recommendations, which can be readily implemented in daily practice. The term "colorectal care bundle," which is widely used in the Anglo-Saxon world, is best translated as "colorectal care bundle."

## II.3. Complications of colorectal surgery

The efficacy of surgical intervention is undoubtedly contingent upon a multitude of variables that are beyond the control of the individual or team performing the procedure. These include the patient's age, gender, anatomical characteristics, stage of the tumour, and the potential for narrowing. It is a well-established fact that a number of factors can be modified to reduce the risk of postoperative morbidity and mortality in patients undergoing surgery. These include weight loss of more than 10%, obesity, anaemia, diabetes, hypoproteinemia, chronic kidney disease, heart disease, regular use of steroids, intraoperative complications or operating time of. Furthermore, it is essential to be aware of these factors and, if possible, to optimise them preoperatively, as this is a key factor in achieving surgical success. In the majority of

cases, colorectal surgery involves the opening of the bowel, during which bacterial contamination may develop. A significant proportion of complications are related to this underlying condition. There are three subgroups of wound infections: superficial, deep and intra-organ. Superficial SSI is defined as an infection that localises to the skin or subcutaneous tissues within 30 days after surgery. Deep tissue SSI is characterised by the involvement of the fascia and muscle layer, resulting in purulent discharge or the division of the abdominal wall. Intra-organ SSI is defined as the presence of purulent discharge through abdominal drainage, the isolation of bacteria from abdominal fluid by sterile sampling, or the confirmation of an intra-abdominal abscess. Other common complications include wound separation, various bleeding complications, postoperative bowel movement disorders (postoperative paralytic ileus), and suture failure, which is one of the most significant consequences of intra-organ SSI. The incidence of wound infections is estimated to be between 5 and 12%, with suture failure occurring in 1.2 to 20.5% of rectal surgeries, according to various studies, and 2.8 to 8.4% of colonic operations. These complications significantly increase mortality, worsen the quality of life of patients and drastically increase the cost of care. It has been demonstrated in numerous disease groups that deviation from a standardised treatment plan is associated with a higher number of recurrences, which in turn leads to a significant deterioration in disease-free survival (DFS) and overall survival (OS). There are several classifications based on the types of complications, of which the widely used Clavien-Dindo classification is particularly useful, as it allows for a systematic and easy comparison of the many different types of complications.

### II.3.a Mechanism of septic complications

A number of factors contribute to the development of surgical site infections (SSIs) in patients who have undergone colorectal surgery. The large intestine contains a vast array of bacteria, including both Gram-

positive and Gram-negative strains, as well as aerobic and anaerobic pathogens. The introduction of these pathogens into the surgical site significantly increases the likelihood of developing a septic complication. In wound infection, the bacterial contamination is also crucial due to the limited capacity of the immune system to eliminate it. A further factor is the infectivity and virulence of the pathogens entering the wound, which depends on the endo- and exotoxins they produce. In the case of prolonged hospitalisation or preventive antibiotic treatment, patients may have been colonised by more virulent pathogens.

The surgical site itself plays an important role in the development of wound infection. By good exploration of the surgical site, careful preparation, good tissue access and precise tissue handling, the rate of wound infection can be reduced. This is one of the principal themes of this thesis. The most severe form of septic complications is suture failure, which is typically caused by excessive tension on the suture and/or lack of adequate circulation around the suture. However, it can also be caused by surgical errors. Suture failure may also be caused by the proteolytic effect of protease, matrix metalloprotease and collagenase produced by bacteria in the intestinal lumen. Surgical stress can result in the predominance of strains that bind to the anastomotic site and then participate in the development of suture failure through their ability to produce proteolytic enzymes. Another key topic of this thesis is the impact of mechanical lining preparation and oral antibiotic prophylaxis on this.

### II.3.b Advanced perioperative care (ERAS)

Correct perioperative management is the most important tool for a successful surgical outcome. The Enhanced Recovery After Surgery (ERAS) protocol, with its evidence-based recommendations, is a constantly updated guiding principle for a multidisciplinary and multidirectional approach to colorectal surgery.

### II.3.c Antibiotic prophylaxis and mechanical bowel preparation

It can be argued that the most crucial and contentious aspect of the immediate preoperative period is the mechanical preparation of the bowel and the utilisation of oral antibiotics. The 2018 ERAS Society Guideline states that MBP (Mechanical Bowel Preparation) alone is not recommended. MBP+OAP (Oral Antibiotic Prophylaxis) is recommended, but only on the basis of weak evidence and with weak recommendations. This represents a small but significant change from the previous recommendation. This is of interest in light of the fact that data from the 2015 US NSQIP National Surgical Quality Improvement Program (NSQIP) has been used by several working groups to process and publish data of great significance since 2016. The majority of these studies found that the combination of MBP+OAP significantly reduces SSI, AL, and POI. In the ASCRS 2023 recommendation, evidence 1B is already available for the co-administration of mechanical preparation and oral antibiotic. The 2019 ASCRS recommendation also states that MBP alone is not recommended (evidence 1A), nor is bowel preparation. Furthermore, enemas alone (evidence 2B) and oral AB use alone (evidence 2C) are not recommended. In 2023, an article was published in the Cochrane Library demonstrating that combined bowel preparation resulted in significantly lower SSI and seam failure rates compared to mechanical bowel preparation alone. In this meta-analysis, the SOAP study material was also processed, and our study was considered to be of high quality. Additionally, in 2023, the rapid guideline of SAGES, EAES and ESCP was published, recommending the use of only oral antibiotic prophylaxis or OABP preparation combined with MBP as an option for right colon surgery. In cases involving other sections of the colon and the rectum, combined lining preparation is clearly recommended. The SOAP study, which was published by this research group, constituted the basis for this guideline.

### II.3.d Early detection of complications

The early detection of complications is of essential importance for the early treatment of surgical patients. The early treatment of surgical patients increases the success and effectiveness of treatment. In the postoperative period, the healing process is monitored by regular physical examinations, laboratory tests and imaging studies. The most common of these laboratory tests is the measurement of C-reactive protein (CRP), an acute phase protein, which is elevated in inflammatory processes. CRP levels normally rise to their highest level on day 2 after surgery and then gradually decrease from day 3. If CRP levels do not fall or continue to rise, this is indicative of an ongoing infection. A CRP taken on postoperative day 3 would be the earliest time point to help determine this. This will be addressed in a later chapter of this thesis.

## III. Objectives

Some of the septic complications following colorectal surgery are due to factors that can be influenced. As a researcher and clinician, I am driven by the need to identify these factors and to know how to prevent them. In order to achieve this, I have conducted a number of studies, including one that looks at the possibility of detecting septic complications as soon as possible and two that examine means of prevention.

In chronological order of publication:

1. A comparison of conventional abdominoperineal rectal extirpation and abdominoperineal rectal extirpation with extralevator in the pronated position using single-centre retrospective data collection.
2. A prospective, randomised, multicentre data collection study was conducted to assess the efficacy of preoperative bowel preparation and



oral antibiotic prophylaxis. The primary and secondary endpoints were wound infection, suture failure, postoperative bowel stricture, 30-day hospital readmission and 30-day mortality.

3. A further study was conducted to detect septic complications as early as possible by examining the correlation between C-reactive protein on day 3 after surgery and the development of septic complications.

#### **IV. The articles that constitute the paper are as follows**

1. G Papp, Gy Saftics, B E Szabó, J Baracs, A Vereczkei, D Kollár, A Oláh, P Mészáros, Zs Dubóczki, A Bursics, Systemic *versus* Oral and Systemic Antibiotic Prophylaxis (SOAP) study in colorectal surgery: prospective randomized multicentre trial, *British Journal of Surgery*, Volume 108, Issue 3, March 2021, Pages 271-276, <https://doi.org/10.1093/bjs/znaa131>
2. Géza Papp, Kristóf Dede & Attila Bursics (2021) Short-term advantages of ELAPE over APR, *Acta Chirurgica Belgica*, 121:5, 327-332, DOI: [10.1080/00015458.2020.1778265](https://doi.org/10.1080/00015458.2020.1778265)
3. Papp G, Vereczkei A, Kollár D, Mersich T, Bursics A. C-Reactive Protein Taken on Postoperative Day 3 Has No Role in Predicting Complications After Elective Colorectal Surgery: an Observational Study from the Randomized Multi-Center Prospective SOAP Trial. *J Gastrointest Surg.* 2022 Dec;26(12):2595-2596. doi: 10.1007/s11605-022-05400-2. Epub 2022 Jul 19. PMID: 35854208.

## V. Results

### V.1. Short-term advantages of ELAPE over APR surgery

Since 2015, our department has been performing rectal extirpations (ELAPE) in a prone position (pronated). Furthermore, the abdominal phase of the surgery is increasingly being performed laparoscopically. In order to ascertain the advantages and disadvantages of the pronated position surgical method for rectal extirpations, a retrospective investigation was conducted. Data from 35 conventional rectal extirpations performed in 2013-2014 were compared with the results of 38 ELAPE surgeries performed in 2015-2016. The incidence of complications, including intraoperative transfusion, operative time, postoperative ileus, and postoperative CRM positivity, as well as minor and major Clavien-Dindo complication groups, were analysed. One of the advantages of our retrospective data analysis was that we could compare the results of surgeries performed by the same surgeons.

Based on our experience, the ELAPE procedure has allowed us to perform a wider and more precise surgical excision of the tumour. The prone position afforded significantly enhanced visibility, enabling more accurate preparation and gentler tissue handling during the perineal phase of the procedure. The perioperative complication rates were lower in the ELAPE group. This significant reduction can be attributed to the transfer from the "minor complications" Clavien-Dindo I and II group to the "no complications" Clavien-Dindo 0 group, as well as a significant reduction in the rate of minor complications. No difference was found in the rate of "major complications" in Clavien-Dindo III-V. Consequently, we examined the complications that were responsible for the significant differences. These were predominantly complications related to the perineal phase. There was a striking difference in the incidence of both intraoperative iatrogenic injuries and postoperative pelvic organ dysfunction. This was attributed to the pronated position, as this position greatly improves access to the surgical site and facilitates wider and more

accurate preparation. In our experience, the IOTP and positive CRM rates were also lower in the ELAPE group, although this did not reach a statistically significant level. We had extensive experience with the conventional Miles procedure, but relatively less with ELAPE in the prone position. We believe that our results could be improved by gaining more experience with the surgical anatomy of the pronated position. In addition, our early oncological results with the Miles operation are quite good and not easy to improve further. The higher rate of gluteus maximus rotator lobe reconstruction indicates a more radical surgical intervention in the ELAPE group. Nevertheless, perineal SSI showed no increase but a decrease, although not significant. This discrepancy can be explained by the fact that better visibility and more precise surgical incisions in the pronated position allowed for better wound healing despite greater destruction and longer surgery. The operative time was significantly longer in the ELAPE group. This is not unexpected, given that conventional APRs employed a double team approach. One team worked within the abdominal cavity, while the other worked on the perineum. In ELAPE, one team is responsible for completing the abdominal phase of the surgery, then turning the patient over and completing the perineal phase. Several laparoscopic procedures were performed in the ELAPE group, which aligns with the current trends in Hungary, where there has been an increase in funding for laparoscopic colorectal surgery. In our experience, the prone position greatly improves visibility during the perineal part of the surgery. This appears to be a subjective conclusion, but in the pronated position, even the coccyx can be removed, allowing a longer incision and wider surgical access to the distal part of the rectum. In contrast, in the traditional lithotomy position, the surgeon has little access to the coccyx. The reduced rate of minor complications may not be reflected in the length of hospital stay, as although preoperative stoma therapy and patient education exist, actual education can begin after surgery. This means that, although theoretical training in ostomy therapy begins before surgery in some centres, practical training takes place after surgery while the patient is still in hospital, thus preventing earlier

discharge of patients who recover uneventfully.

## V.2. The combined use of mechanical lining and oral antibiotic prophylaxis

The SOAP2016 study prospectively investigated the impact of MBP and OABP on SSI, AL, POI, 30-day hospital readmission and mortality. Our study confirmed that OABP used in conjunction with MBP significantly reduces postoperative SSI after elective colorectal resection with anastomosis formation, irrespective of the success rate of MBP. This effect was most marked in the proportion of superficial SSI, but was also observed in deep and abdominal SSI. The data also confirm that OABP in combination with MBP significantly reduces the rate of suture failure. This effect appears to be from the BBPS $\geq$ 2 subgroup, i.e. the subgroup of successfully prepared patients. In our study, the combination of OABP and MBP did not reduce the incidence of POI. This may be related to the lower, than expected incidence of POI in the study, which may be a result of the use of ERAS protocols at all four participating institutions.

Multivariate linear regression analysis showed that three factors influence the incidence of SSI: OABP, BBPS score $\geq$ 2 and use of minimally invasive technique. Among these factors, the administration of OABP also significantly reduced the rate of suture failure. It has been demonstrated that rectal anastomosis significantly increases the risk of suture failure. The frequency of POI was found to be associated with male gender and history of COPD. Furthermore, 30-day mortality was found to be significantly more frequent when a rectal anastomosis was performed and when intraoperative surgical or anaesthetic complications occurred. In addition, 30-day hospital readmission was found to be significantly more frequent for COPD and significantly less frequent for laparoscopic (MIS).

Given that the mechanical preparation of the intestine was not always optimal, a subgroup study was conducted to investigate the potential benefits of OABP administration in terms of the success of the intestinal

preparation. When examining SSI, it was confirmed that OABP significantly reduces SSI in both successful and unsuccessful bowel preparation. Furthermore, we found that in cases where the patient does not receive OABP, successful MBP alone reduces SSI. With regard to suture failure, it can be concluded that successful MBP in conjunction with OABP significantly reduces the incidence of suture failure. Oral antibiotics administered on the day prior to surgery had no effect on POI, 30-day mortality or 30-day hospital readmission.

### V.3. Postoperative day 3 C-reactive protein has no role in predicting complications after elective colorectal surgery

The C-reactive protein (CRP) value on postoperative day 3 is a commonly used method in clinical practice as a marker of surgical site infection (SSI) and acute lung injury (ALI). Higher CRP values indicate the presence of infection. In our study, we tested the appropriateness and reliability of this method in a multicentre, prospective observational clinical trial. Our aim was to determine an early time point, therefore we chose POD 3 for CRP assessment. The results demonstrated that although there were differences in CRP between the uncomplicated and complicated groups, these were not statistically significant. Furthermore, the variance was so large that no correlation could be established, and it was not possible to separate the groups based on ROC curves.

Our study indicates that CRP measured during POD3 has a low prognostic value with regard to safe early discharge or the prediction of septic complications.

## VI. Discussion

### VI.1. Comparison of conventional abdominoperineal rectal extirpation and abdominoperineal rectal extirpation with extralevator in the pronated position using single-center retrospective data collection

The ELAPE study compared the complication rates of the two surgical groups and found no significant reduction in perineal regional SSI, but a significant benefit in intraoperative breast injury and postoperative functional impairment in favour of ELAPE in the pronated position. The reason for the lower rate of functional impairment in the pronated position is that the pelvic anatomy can be more accurately identified, which is associated with a lower rate of iatrogenic injuries. Although the ELAPE study demonstrated a non-significant reduction in perineal wound infections, several factors may be responsible. The advantage of the pronated position allows for a wider excision with flap rotation and replacement. However, because of this, a higher wound-related complication rate would be expected. Nevertheless, the better exploration in the pronated position resulted in an overall lower SSI rate compared to the control group.

**Table 5.** Number of surgical complications in connection with the perineal dissection.

	APR (N = 35)	ELAPE (N = 38)	p-value
Perineal SSI	13 (37.1%)	10 (26.3%)	.320 Chi-square test
Intraoperative iatrogenic injury	6 (17.1%)	1 (2.6%)	.035 Chi-square test
Postoperative pelvic organ dysfunction	7 (20.0%)	1 (2.6%)	.018 Chi-square test

During ELAPE surgery, the perineal section is prepared in a prone pronated knife position. The effect of this on the surgical technique is that it allows a more accurate and precise preparation, and therefore the rate of mild but frequent minor complications is significantly reduced in favour of cases without complications.

**Table 3.** Primary endpoints.

	APR (N = 35)	ELAPE (N = 38)	p value
Intraoperative perforation (IOTP)	4 (11.4%)	3 (7.9%)	.608 Chi-square test
CRM positivity	4 (11.4%)	3 (7.9%)	.608 Chi-square test
Postoperative complications (Clavien-Dindo classification)			
No complication (0)	8 (22.9%)	21 (55.3%)	.01 Chi-square test
Minor (I-II)	19 (54.2%)	9 (23.7%)	
Major (III-V)	8 (22.9%)	8 (21.0%)	

The prone, jackknife position can be employed to excise the tumour and to cover the defect with a flap. However, this position is not only useful for extensive rectal cancers. As it provides greater exposure and easier surgical access, this position is also useful in surgery for localised rectal cancers. As the mesorectal adipose tissue around the lower third of the rectum thins, lower third rectal cancers are getting closer to the levator muscle and are at risk of negative CRM. In fact, in the lithotomy position, we frequently encounter the challenge that the excised specimen exhibits the thinnest perirectal tissue precisely where the tumour is located. Consequently, it is often challenging to perform oncologically appropriate surgery in the standard lithotomy position. One solution to this problem is to perform surgery in the supine jackknife position. This approach has several advantages, including the ability to avoid the aforementioned issue. Additionally, ELAPE performed in the supine jackknife position has several oncological and technical advantages.

In the lithotomy position, the CRM positivity rate is around 10-30% in the literature. In contrast, in the supine jackknife position, this rate is only 10%. In the lithotomy position, the IOTP rate is 10-30%, compared to 5-10% in the supine jackknife position. The relative risk reduction for local recurrence after surgery in the supine jackknife position was found to be 39% in A meta-analysis published in 2012 indicated that ELAPE has oncological advantages over the conventional approach. In contrast, an analysis of the Danish database found a higher CRM positivity rate in the ELAPE group, and an analysis of the Swedish national database found a significantly increased 3-year local recurrence rate after ELAPE compared to conventional APR. There is a considerable body of evidence indicating that total levator muscle extirpation is associated with

significantly increased complication rates. However, there are several studies that challenge these findings. We employed the personalised radical ELAPE procedure and observed that the complication rate was reduced, while the short-term oncological data remained essentially unchanged.

*VI.2. A prospective, randomised, multicentre data collection study of the efficacy of preoperative lining preparation and oral antibiotic prophylaxis: the SOAP trial*

Both the colorectal care bundle and the ERAS protocol define the recommended approach to be taken in each phase of surgery. Both recommendations aim to reduce complication rates through a multimodal approach. The colorectal care bundle analyses colorectal surgery primarily from a surgical perspective, while the widely known and regularly updated ERAS protocol takes a multidisciplinary approach to the perioperative phase.

Mechanical bowel preparation and oral antibiotic prophylaxis are key issues in the preoperative care phase. In our own research, we primarily investigated the efficacy of oral antibiotics in the SOAP trial. Of the two study arms in the SOAP trial, patients in one arm received only mechanical bowel preparation, while patients in the other arm received mechanical bowel preparation combined with oral antibiotics.



Table 2 Intraoperative and postoperative complications

	Oral antibiotic prophylaxis (n = 253)	No oral antibiotic prophylaxis (n = 276)	z	P <sup>†</sup>
<b>Intraoperative anaesthetic complication</b>	17 (6.7)	11 (4.0)	1.40	0.081
<b>Complications by Clavien-Dindo grade</b>				0.689 <sup>†</sup>
0	158 (62.5)	167 (60.5)		
I	41 (16.2)	42 (15.2)		
II	31 (12.3)	44 (15.9)		
IIIa	2 (0.8)	1 (0.4)		
IIIb	11 (4.3)	14 (5.1)		
IVa	6 (2.4)	4 (1.4)		
IVb	1 (0.4)	0 (0)		
V	3 (1.2)	4 (1.4)		
<b>Clostridium difficile infection</b>	4 (1.6)	2 (0.7)	0.92	0.176
<b>Overall SSI</b>	8 (3.2)	27 (9.8)	-3.06	0.001
<b>Superficial SSI</b>	6 (2.4)	18 (6.5)	-2.29	0.011
<b>Deep SSI</b>	1 (0.4)	4 (1.4)	-1.25	0.105
<b>Organ space SSI</b>	1 (0.4)	5 (1.8)	-1.53	0.061
<b>Postoperative ileus</b>	16 (6.3)	16 (5.8)	0.25	0.343
<b>Anastomotic leak</b>	4 (1.6)	13(4.7)	-2.03	0.020
<b>Hospital readmission</b>	12 (4.7)	10 (3.6)	0.64	0.251
<b>Mortality</b>	3 (1.2)	4 (1.4)	-0.26	0.397

Values in parentheses are percentages. SSI, surgical-site infection. \* z test, except <sup>†</sup>χ<sup>2</sup> test.

The comparison of the two groups confirmed that there was a significant difference between the two groups in terms of total wound infection, superficial SSI and suture failure. Multivariate analysis identified three independent factors that significantly reduced the incidence of wound infections: oral antibiotic preparation, mechanical lining preparation and use of laparoscopic technique. Male infants and chronic obstructive pulmonary disease (COPD) were identified as significant risk factors for postoperative ileus, which was an additional primary endpoint. The incidence of suture failure was significantly lower in the group that received oral antibiotic prophylaxis, but higher when anastomosis was applied to the rectum. Our results indicated a significant positive association between rectal anastomosis and any intraoperative surgical or anaesthetic complication in terms of 30-day perioperative mortality. Furthermore, the 30-day hospital readmission rate was significantly higher in COPD patients and significantly lower in those who underwent laparoscopic surgery.

**Table 3 P values from multivariable linear regression analysis of the effect of demographic and clinical variables on primary and secondary endpoints**

	P				
	SSI	Postoperative ileus	Anastomotic leakage	Mortality	Hospital readmission
Age > mean (66.3 years)	0.437	0.464	0.127	0.170	0.287
BMI > mean (27.2 kg/m <sup>2</sup> )	0.391	0.391	0.174	0.307	0.421
Male sex	0.249	0.005	0.479	0.171	0.083
Cardiac disease	0.357	0.246	0.061	0.334	0.447
Diabetes mellitus	0.464	0.464	0.323	0.402	0.297
COPD	0.406	0.040	0.083	0.348	0.020
Anticoagulant therapy	0.083	0.153	0.347	0.446	0.161
Oral antibiotic prophylaxis	<0.001	0.332	0.048	0.392	0.256
BBPS score ≥ 2	0.052	0.190	0.481	0.106	0.242
Laparoscopic surgical access	0.003	0.121	0.337	0.252	0.031
Rectal anastomosis	0.118	0.207	0.001	0.031	0.232
Neoadjuvant therapy	0.461	0.216	0.208	0.133	0.116
Intraoperative surgical complication	0.164	0.336	0.404	0.024	0.581
Intraoperative anaesthetic complication	0.093	0.321	0.173	0.002	0.203

SSI, surgical site infection; COPD, chronic obstructive pulmonary disease; BBPS, Boston Bowel Preparation Scale.

In our comprehensive analysis of the dataset, we also examined a number of correlations that were not initially identified as primary research objectives. While the primary objective of the SOAP study was to assess the efficacy of preoperative oral antibiotic use, the data also provided a novel focus for evaluating the effectiveness of mechanical bowel preparation. In the SOAP study, mechanical bowel preparation was performed in all cases, but in nearly 40% of cases it was not fully successful (BBPS≤1). This circumstance also provided an opportunity to perform subgroup studies. The objective of the subgroup analysis was to determine the significance of the success of mechanical bowel preparation and oral antibiotic prophylaxis for wound infection and suture failure. The results demonstrated that oral antibiotic prophylaxis with successful bowel preparation (BBPS≥2) significantly reduced both SSI and suture failure. Conversely, if bowel preparation was unsuccessful (BBPS≤1), oral antibiotic prophylaxis only significantly reduced SSI. The data indicate that, in the absence of oral antibiotic prophylaxis, good lining preparation alone significantly reduces SSI.

**Table 4** Subgroup analyses of impact of success of mechanical bowel preparation on surgical-site infection and anastomotic leak rates

	No. of patients	BBPS score $\geq 2$ (n = 328)	BBPS score $\leq 1$ (n = 129)	z	P*
<b>Surgical-site infection</b>					
Oral antibiotic prophylaxis	217	5 of 159 (3.1)	3 of 58 (5)	-0.70	0.242
No oral antibiotic prophylaxis	240	14 of 169 (8.3)	11 of 71 (15)	-1.67	0.047
z		-1.99	-1.87		
P*		0.023	0.031		
<b>Anastomotic leak</b>					
Oral antibiotic prophylaxis	217	1 of 159 (0.6)	2 of 58 (3)	-1.57	0.058
No oral antibiotic prophylaxis	240	10 of 169 (5.9)	3 of 71 (4)	0.53	0.298
z		-2.66	-0.23		
P*		0.004	0.409		

Values in parentheses are percentages. BBPS, Boston Bowel Preparation Scale. \* z test.

The issue of perioperative bowel preparation, including mechanical bowel preparation and OABP, has long been a controversial topic among colorectal surgeons. In the past decades, the studies available in the literature were not precise enough and the results were highly variable. More recently, Espin-Basany and colleagues conducted a single-centre study which did not demonstrate an influence of OABP on SSI. However, they reported gastrointestinal side effects in up to 40% of patients receiving OABP. In our own study, the side effects of OABP were mild, with only 2.3% of patients stopping study medication. Espin-Basany and colleagues observed that diabetes did not affect the complication rate, but COPD did – as in our present study.

In a study of 500 patients at 10 Japanese centres using oral kanamycin and erythromycin, Kobayashi and colleagues concluded that OABP does not prevent SSI in elective colorectal cancer surgery. However, their published data (using a z-test) showed significantly fewer cases of SSI in the OABP+ group. The investigators examined the impact of OABP in rectal surgery and discovered that the prevalence of superficial SSI following abdominoperineal rectal resection (APRE) was diminished with the use of OABP.

In a recently published prospective study in Finland, patients receiving MBP and OABP were compared with patients not receiving lining preparation (NoPrep). Despite the NoPrep group exhibiting a nearly 50% higher complication rate (7% versus 11%), the authors concluded that

there was no significant difference between the two groups. This result is likely attributable to the fact that the study was not powered to detect a 4% difference.

In 2015, a series of studies based on ACS NSQIP data indicated that MBP reduces SSI, POI, AI rates and reduces 30-day mortality. The combination of OABP and MBP further improved results, with tens of thousands of patients included in all studies and similar results found. Although the analysis was retrospective, the number of patients included in the studies was considerable.

In a subsequent meta-analysis of randomised trials published since 1981 and some cohort studies, Toh et al. made direct and indirect comparisons between OABP+MBP, MBP only, OABP only and NoPrep groups. They found a significant reduction in SSI cases in the OABP+MBP group, but no difference in AI, mortality or hospital readmission. Rollins et al. conducted a meta-analysis using data from 40 studies and 69,517 patients, and concluded that OABP alone or in combination with MBP significantly reduces SSI. Chen et al. found that iv prophylaxis with OABP and MBP significantly reduced the incidence of SSI after elective colorectal surgery compared to iv antibiotics with MBP alone. McSorley et al. analysed 22 trials involving 57,207 patients and concluded that OABP combined with MBP and intravenous antibiotics was superior to MBP and intravenous antibiotic prophylaxis alone in reducing SSI after elective colorectal resection. Based on the included trials, this prophylaxis was associated with a significantly lower incidence of both AI and POI, as well as a lower reoperation rate, length of hospital stay, readmission and mortality. Since 2021, several meta-analyses have been published in which the SOAP trial was already an active participant. Yue et al. published in 2023, which looked at 8852 patients from 22 RCTs comparing MBP and combined MBP+OABP. Their analysis concluded that the incidence of SSI and AI was significantly lower in the combined MBP+OABP group. In 2023, Castagneto et al. conducted a meta-analysis to investigate the influence of different antibiotic prophylaxis on the incidence of surgical site infection (SSI) and anastomotic leak (AL).

Their analysis supported the use of oral antibiotic administration, but could not comment on its exact form, and recommended further studies. Tan et al. (2023) reviewed 60 RCTs to investigate the benefits of injectable preparation. In comparison to intravenous antibiotic prophylaxis alone, the combination of intravenous and oral antibiotic prophylaxis with mechanical lining and oral antibiotic prophylaxis (OABP) demonstrated a significant reduction in the incidence of surgical site infection (SSI) and seam failure. Conversely, the administration of systemic antibiotics (AB) alone was associated with an increased incidence of SSI, while mechanical bowel preparation (MBP) alone did not affect the incidence of AI. However, these findings could not be corroborated in the SOAP study. Our results suggest that the administration of MBP alone, in conjunction with systemic antibiotic prophylaxis, may reduce the incidence of SSI and have no effect on AI. Koo (2023) meta-analysis included 46 studies. The study demonstrated that the incidence of SSI with OABP is significantly lower. Furthermore, the combination of neomycin+ metronidazole and neomycin+ kanamycin was found to be more effective than neomycin+ erythromycin.

A Cochrane Library systematic review and meta-analysis was published in February 2023. The aim of this review was to investigate the benefit of MBP+OABP in the prevention of complications. 5264 patients from 21 RCTs were included. The authors conclude that, based on moderate evidence, MBP+OABP is probably more effective in preventing postoperative complications than MBP alone. In particular, the complication rates were lower for SSI and suture failure. It could not comment on whether OABP alone would be equivalent to MBP+OABP.

EAES, SAGES and ESCP published a joint guideline in 2023, in which recommendations, randomised trials and meta-analyses published since 2000 were analysed and recommendations made by a panel of experts.

- OABP is recommended for right colon MIS surgery, alternatively MBP+OABP can be used together.

- The use of MBP+OABP is recommended prior to MIS right colon resection surgery if intracorporeal anastomosis is intended.
- MBP+OABP+ enema is recommended for MIS rectal surgery.
- MBP+OABP is recommended before MIS left colon and sigmoid colon surgery.
- The recommended use of MBP+OABP is recommended for any MIS colon and rectal surgery when intraoperative localisation is required.

The joint recommendation also stated that, on the basis of current evidence, no new clinical trials are expected to require a change to this guideline in the near future.

*VI.3. Screening for early detection of septic complications, C-reactive protein on day 3 postoperatively and the development of septic complications*

In accordance with the general preventive approach of medicine, all specialties are seeking to identify indicators that may assist in the identification of cases of risk. A multitude of different methods and markers are employed to detect complications at various stages. The literature indicates that early suspicion of a complication underlying the indicator signal leads to earlier detection. Various studies have reported the results of C-reactive protein (CRP), white blood cell count, serum procalcitonin, interleukins, tumour necrosis factor alpha and drainage secretion measurements over a wide time interval, mostly between days 3 and 7 post-intervention. A widely and easily available, inexpensive method is the measurement of C-reactive protein (CRP), which is elevated with a 48-hour delay in inflammatory processes. The evaluation of CRP at POD 3 as a marker of SSI and AL is a common method in clinical practice. According to the relevant literature, a higher CRP value indicates the presence of infection. In this study, we tested the

appropriateness and certainty of this method by analysing data from a multicentre prospective observational clinical trial.

In the SOAP study, we investigated the association between postoperative day 3 CRP and the incidence of septic complications. ROC curve analysis was performed, and the results are presented in the following table. The area under the curve (AUC) values for the association between CRP on day 3 and the development of complications were 0.79 (cut-off: 138 mmol/l) for all septic complications, 0.57 (cut-off: 244 mmol/l) for suture failure, and below 0.80 for all AUCs, indicating that there was no clear association between CRP on day 3 and the development of complications. The reason why the AUC values were low may be due to the wide range of CRP values in the complication groups.

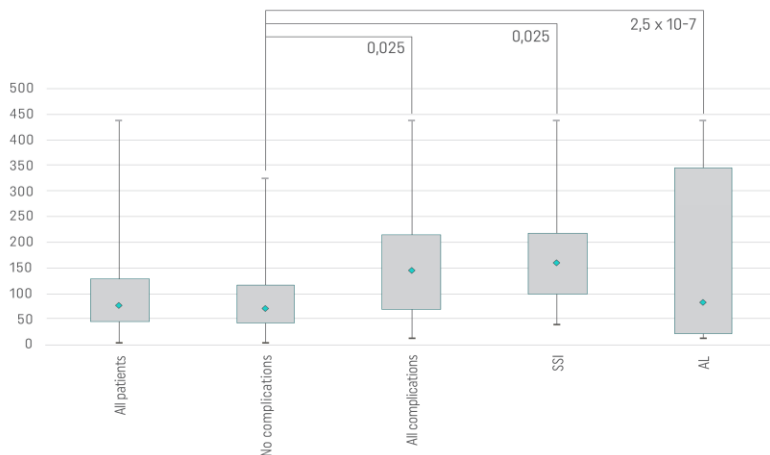


Figure 2. The CRP values of the patients are presented graphically as a box plot diagram, chi square test values are in staple lines.

The occurrence of septic complications following colorectal resection

has been demonstrated to affect both short-term survival and the oncological outcome. Consequently, the objectives of postoperative investigations are different. Such tests can assist in decisions regarding early discharge, while also providing an early warning of serious complications. There is a clear clinical need for a parameter that can aid these decisions; a simple laboratory test may be the most beneficial solution. Previous studies have examined CRP levels at different postoperative days (3,4,5) and found different cut-off values with different negative and positive predictive values. However, only a small proportion of these studies were prospective, and the case numbers were low. A number of studies have examined CRP levels at different postoperative days (3,4,5) and identified different cut-off values with varying negative and positive predictive values. However, only a small proportion of these studies were prospective, and the case numbers were low. A number of studies have indicated that the sensitivity of CRP is variable. The majority of these studies have confirmed the association between elevated CRP and septic complications. However, there is a general consensus that CRP levels on POD 3 alone are not sufficient for the early diagnosis of complications and that consideration of the overall clinical status is essential.

The analysis of the results did not demonstrate that CRP measured on day 3 is a predictor of septic complications. Furthermore, due to the very large variation in CRP values, it was not possible to find evidence that CRP on day 3 could be used to select cases that were definitely free of complications. The limitations of this study include the low rates of SSI (5.7%) and AL (3.2%) observed in the study cohort, which were both below the rates reported in the literature. While this was beneficial for the study's outcomes, it also posed challenges in statistical analysis due to the small size of the complication groups.

The objective of this study was to identify an early time point for CRP assessment. To this end, we chose POD 3 as the optimal time point for CRP measurement. Many studies recommend measuring CRP later (e.g. POD 4 or POD 5), but in the minimally invasive era, patients are no



longer in the hospital for testing by this time. In order to select the optimal biomarker and the most predictive time window for subsequent complications, a study protocol with multiple inflammatory markers and a wider time window needs to be processed.

The findings of the study reinforce the long-standing medical view that a laboratory result should not be regarded as a substitute for clinical assessment and a careful patient examination.

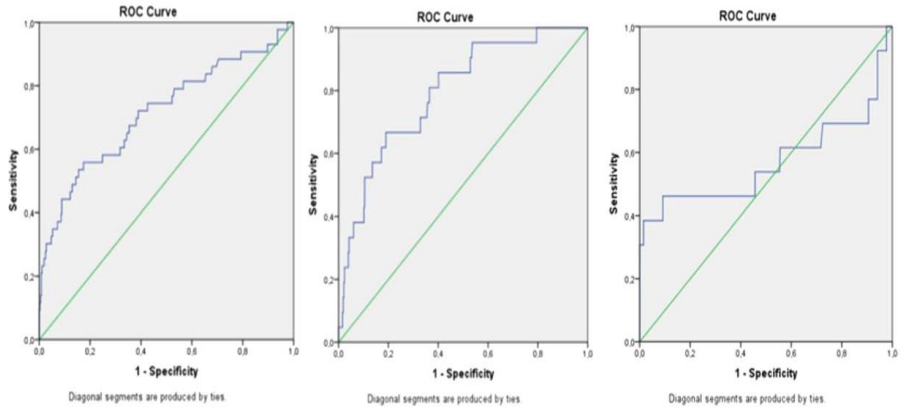


Fig.1 All septic complications, SSI, and AL at POD3 (ROC analysis)

Table 1 AUC and calculated values of the ROC curves

	AUC	Cut off values	Sensitivity	1-Specificity	NPV	PPV
All complications	0.715	138.05	0.5881	0.174	0.9402	0.2758
SSI <sup>a</sup>	0.794	138	0.667	0.19	0.9780	0.1610
AL <sup>b</sup>	0.569	244	0.385	0.015	0.9797	0.4598

<sup>a</sup>Surgical site infections. <sup>b</sup>Anastomosis leaks

## **VII. Conclusion, new results**

The results of the ELAPE study indicate that the MIS method is applicable and advantageous in the abdominal phase of rectal resections. Our findings demonstrate that approaching the perineal tract in the pronated position is associated with significantly less iatrogenic injury, better functional outcomes, while not increasing the rate of wound complications and not affecting the short-term oncological benefit.

The SOAP study demonstrated that the administration of oral antibiotics (OABP) on the day prior to surgery in conjunction with mechanical bowel preparation (MBP) can effectively reduce the incidence of surgical site infections (SSI) and anastomotic leaks (AL) following elective colorectal resection. Oral antibiotics given on the day prior to surgery had no effect on post-operative ileus (POI), 30-day mortality or 30-day hospital readmission. The use of OABP in the setting of failed bowel preparation was found to significantly reduce SSI. Of the 24 references published since the SOAP trial was published in April 2021, 10 have been cited in a meta-analysis, peer-reviewed journal. Of these, the most notable is its inclusion in the Cochrane Library, where the SOAP trial was considered to be of very high reliability, precisely conducted, and its results were consistent with the conclusion and greatly influenced the conclusion of the meta-analysis. Additionally, the rapid guideline on liner preparation, published jointly by EAES ESCP in 2023, is of significant importance. This guideline also includes the SOAP study as background material. This is the first European guideline to advocate the combined use of OABP and MBP.

The study on the prediction of septic complications demonstrated that no positive or negative predictive conclusion can be drawn from CRP values measured on postoperative day 3. Given the considerable variability in CRP values, this biomarker cannot be relied upon as a reliable basis for the early detection of SSI or AI. Furthermore, it is not a useful tool for the early diagnosis of complications or the early isolation of uncomplicated cases.

## VIII. Acknowledgements

Throughout my medical career, I have met many friends, colleagues and teachers to whom I owe my scientific determination and perseverance. It is impossible to list them all, but I think of them all with sincere gratitude. But I must mention a few people in particular.

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I also owe a special debt of gratitude to my wife and children for always supporting me when I was tired and giving me strength. My wife Márta also started her research career as an adult. Her doctoral school was the first one I learned from. It was then that I started to learn the basics of research thinking. Márta's perseverance and enthusiasm was a constant inspiration for my work later on. Scientific work has become part of our family life, and our children, Dóri and Réka, have patience for it. I also

owe a debt of gratitude to my parents, who have always inspired me with their interest and encouraged me in my work by their example.

## **IX. Publications on which the thesis is based**

1. G Papp, Gy Saftics, B E Szabó, J Baracs, A Vereczkei, D Kollár, A Oláh, P Mészáros, Zs Dubóczki, A Bursics, Systemic *versus* Oral and Systemic Antibiotic Prophylaxis (SOAP) study in colorectal surgery: prospective randomized multicentre trial, *British Journal of Surgery*, Volume 108, Issue 3, March 2021, Pages 271-276, <https://doi.org/10.1093/bjs/znaa131> **SRJ ind: D1, IF: 11,782**
2. Géza Papp, Kristóf Dede & Attila Bursics (2021) Short-term advantages of ELAPE over APR, *Acta Chirurgica Belgica*, 121:5, 327-332, DOI: [10.1080/00015458.2020.1778265](https://doi.org/10.1080/00015458.2020.1778265) **SRJ ind: Q3, IF: 0.99**
3. Papp G, Vereczkei A, Kollár D, Mersich T, Bursics A. C-Reactive Protein Taken on Postoperative Day 3 Has No Role in Predicting Complications After Elective Colorectal Surgery: an Observational Study from the Randomized Multi-Center Prospective SOAP Trial. *J Gastrointest Surg.* 2022 Dec;26(12):2595-2596. doi: 10.1007/s11605-022-05400-2. Epub 2022 Jul 19. PMID: 35854208. **SRJ ind: Q1, IF: 3.2**

**Total IF of the author: 16,885**

## **X. Presentations related to the publication**

1. 2010 Fresenius Anaesthesiologist Day, Cegléd Fast Track

- Surgery Hungarian speaker
2. 2010 MST, Siófok Fast Track Surgery Hungarian speaker
  3. 2010 MST, Siófok Laparoscopic colorectal surgery Hungarian lecturer
  4. Hajduszoboszlo Laparoscopic colorectal surgery introduction in our department Hungarian lecturer
  5. 2011 Advanced laparoscopy course, Budapest Laparoscopic rectum extirpation Hungarian organizer and lecturer
  6. 2011 Advanced Laparoscopy Course, Budapest Fast Track Surgery- Percutaneous Surgery Hungarian lecturer
  7. 2012 MST, Szeged Laparotomy or laparoscopy? Traditional or Fast track?
  8. 2014 Hungarian Congress of Coloproctologists Cilindrical abdomino-perineal rectal extirpation Hungarian speaker
  9. 2014 MST, Budapest Cilindrical abdomino-perineal rectal extirpation Hungarian speaker
  10. 2014 MST, Coloproctology Section Congress, Antibiotic Prophylaxis, Severe Infection in Colorectal Surgery Hungarian speaker
  11. 2015 Nutricia Masterclass Benefits of early enteral feeding based on the latest ERAS recommendations Hungarian speaker
  12. 2015 MST SES Congress, Eger, Hungary, Minimally invasive strategy for the treatment of diverticulitis perforations Hungarian speaker
  13. 2017 MST COLOPROCTOLOGICAL SECTIONS Congress, Budapest Antibiotic prophylaxis, Severe colorectal infection in colorectal surgery Hungarian speaker
  14. 2017 MST Coloproctology Section ESCP masterclass English organiser
  15. 2017 MST Surgical Oncology Section Congress, Szeged Rectum adenocarc. Quantitative and qualitative changes in the surgical management of cancer in our department between 2011 and 2015 Hungarian co-presenter

16. 2018 MST Congress Debrecen Abdomino-perineal rectal extirpation analysis Hungarian speaker
17. 2019 MMTT Congress Visegrád Fast Track Surgery Hungarian speaker
18. 2021 MST Oral antibiotic prophylaxis in colorectal surgery, SOAP Trial results
19. 2023 MMTT Congress, Visegrád, Enteral feeding before and after bowel surgery